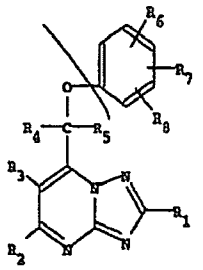
95-161726/21 B02 BOOT 93.10.13
BOOTS CO PLC *WO 9510521-A1
93.10.13 93GB-021162 *(95.04.20)* C07D 487/04, A61K 31/505 (C07D 239:00, 249:00, 487/04)

New and use of 1,2,4-triazolo[1,5-a]pyrimidine cpds. - for treatment and/or prevention of seizures, epilepsy and neurological damage e.g. stroke, brain trauma, head injury or haemorrhage (Eng)

C95-074901 N(AM AT AU BB BG BR BY CA CH CN CZ DE DK EE ES FI GB GE HU JP KE KG KP KR KZ LK LR LT LU LV MD MG MN MW NL NO NZ PL PT RO RU SD SE SI SK TJ TT UA US UZ VN) R(AT BE CH DE DK ES FR GB GR IE IT KE LU MC MW NL OA PT SD SE SZ)

Addnl. Data: HEAL D J, FERNANDEZ FERNANDEZ M I, SARGENT B 94.10.12 94WO-EP03364

B(6-D9, 14-J7, 14-N16) .3



(II)

prepn.

1,2,4-triazolo[1,5-a]pyrimidine cpds. of formula (II) and their salts are new;

$R_1$ = H or 1-6C alkyl, 1-6C alkoxy or 1-6C alkanoyl opt. substd. by one or more of halo, CN, OH or $NH_2$;

$R_2$, $R_3$ = H or 1-6C alkyl, 1-6C alkoxy, 1-6C alkanoyl, 1-6C alkylthio, 1-6C alkylsulphinyl or 1-6C alkylsulphonyl opt. substd. by one or more of halo, CN, OH or $NH_2$;

$R_4$, $R_5$ = H, 1-6C alkyl, opt. substd. by one or more of halo, CN, OH, $NH_2$ or 1-6C alkyl; or

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$CR_4R_5$ = 3-6C cycloalkylidene opt. substd. by one or more of halo, CN, OH, $NH_2$ or 1-6C alkyl;

$R_6$, $R_7$, $R_8$ = H, halo, OH, SH, CN or 1-6C alkyl, 1-6C alkanoyl, 1-6C alkoxy, 2-6C alkoxycarbonyl, carboxy, 1-6C alkanoyloxy, 1-6C alkylthio, 1-6C alkylsulphinyl, 1-6C alkylsulphonyl, 1-6C alkylsulphonylamino, sulphamoyl, carbamoyl, 2-6C alkylcarbamoyl or 1-6C alkanoylamino opt. substd. by one or more of halo, CN, OH or amino and any N atom is opt. substd. by one or more 1-6C alkyl;

with the proviso that if $R_1$, $R_2$, $R_3$, $R_4$ and $R_8$ = H; $R_5$ = Me and either $R_6$, $R_7$ = H or $R_6$ = 4-chloro and $R_7$ is H or 2-chloro then cpd. (II) is not a racemate.

Also claimed is the use of cpds. (I), which are cpds. (II) excluding the proviso, as pharmaceuticals.

USE

Cpds. (I) and (II) can be used for the treatment, prophylaxis and/or inhibition of seizures, neurological disorders such as epilepsy and/or conditions in which there is neurological damage, e.g. stroke, brain tumour, head injuries and haemorrhage. Cpds. (I) and (II) potentiate GABA-A transmission and/or activate neuronal $K^+$ channels.

Admin. may be oral, rectal, parenteral or topical. Typical unit dosage is 1-1,000 mg. pref. 5-500 mg.

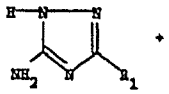
SPECIFIC COMPOUNDS

21 cpds. (I) are claimed. e.g.:
7-[1-(4-fluorophenoxy)ethyl]-1,2,4-triazolo[1,5-a]pyrimidine (IIa);
7-[1-(4-methylsulphonylphenoxy)ethoxy]-1,2,4-triazolo [1,5-a]pyrimidine;
7-[1-(2-chloro-4-fluorophenoxy)ethyl]-1,2,4- triazolo[1,5-a]pyrimidine.

PREPARATION

Cpds. (II) are prepd. as follows (claimed):

(a)



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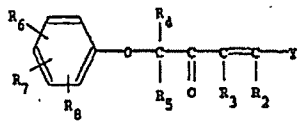
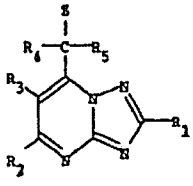
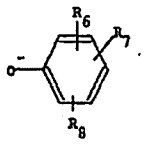


(II)

Y = a leaving gp.

(b)





(II)

Z = a leaving gp.

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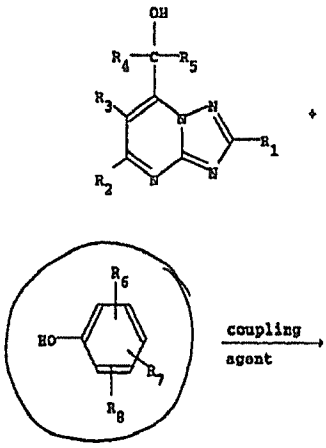
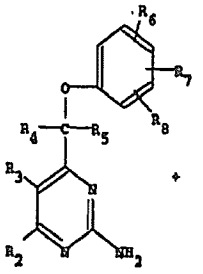
(con't)

(c)



coupling agent → (II)

(d)





$R_1CN \rightarrow O$ —acid catalyzed cyclization→ (II) where $R_1$ is not H

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EXAMPLE

1.12g of 4-fluorophenol was added to a stirred suspension of 0.48 g of NaH in 35 ml of dry 1,2-dimethoxyethane. The mixt. was stirred at room temp. for 30 mins., then a soln. of 2.27 g of 7-(1-bromoethyl)-1, 2, 4-triazolo[1, 5-a]pyrimidine in 85 ml of dry 1, 2-dimethoxyethane was added dropwise. The mixt. was stirred at room temp. for 24 hrs.. The NaBr was removed by filtration.

The solvent was evapd. and the residue dissolved in $CH_2Cl_2$ and washed with 200 ml of a 5% aq. soln. of NaOH, followed by water. The organic layer was dried ($MgSO_4$) and worked up to give 1.03 g of (IIa) m.pt. 106-108 °C. (AC)

(81pp2268DwgNo.0/0)

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